EDITORIAL

New doors to open…and so many!

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Summary

The pursuit of science is a wonderful journey of discovery along which there are a myriad of avenues to be explored. There have always been so many objects

making the decision about which problem to address and then having the self-discipline to explore it in depth challenge all who practice the art. How then are we, as cell biologists, to cope with the mountain of information that is accumulating as we enter the twenty-first

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century? We now have the potential to decipher the primary sequences of every single cellular protein for several model organisms. Just how are we to put this information into an intelligible framework for understanding cell physiology? The turn of a century is a time at which we can permit ourselves the luxury of looking backwards as well as forwards. Where were we a century ago, what were the challenges that faced us then and how do these questions relate to our future goals? As a cell biologist standing on the threshold of the twentieth century, one must have had a similar feeling of elation and expectation to that which we have at the present time. The Theory of Cells had been established by Schleiden and Schwan in 1838–1839, and in the following fifty years it had led to unifying ideas about the nature of plants and animals, an understanding of embryonic development, and the mysteries of the fertilisation of the egg and genetic continuity in terms of ‘cellular immortality’. These were truly halcyon days. By the end of the nineteenth century many of the central principles of cell biology were firmly established. Virchow had maintained in 1855 that every cell is the offspring of a pre-existing parent cell, but the realisation that the cell nucleus is essential for this continuity had to wait another 30 years. By this time, Miecher had already made in 1871 his famous discovery of nuclein, a phosphorus-rich substance extracted from preparations of nuclei from sperm and pus cells, and over the next twenty years a spectrum of sophisticated dyes became available that facilitated the visualisation of not only nuclein but also asters, spindle fibres, and microsomal components of cytoplasm in fixed preparations of cells. The centrosome, discovered independently by Flemming in 1875 and Van Beneden in 1876, and named by Boveri in 1888, was already considered to be an autonomous organelle with a central role in cell division. The behaviour of chromosomes, centrosomes, astral fibres and spindle fibres throughout mitosis and meiosis had been described in exquisite detail. Galeotti had even concluded by 1893 that the unequal distribution of chromatin in cancer cells correlates with an inequality of

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the centrosomes and the development of abnormal spindles - a conclusion reinforced by others over a century later (Pihan et al., 1998; Lingle et al., 1998). It had taken 200 years following Leuwenhoek's first observation of sperm to Hertwig's demonstration in 1875 that fertilisation of the egg is accomplished by its union with one spermatozoon. This demonstration was rapidly followed by Van Beneden's discovery - eventually to unify genetics and cell biology - that the nuclei of germ cells each contain one half the number of chromosomes characteristic of body cells. By 1902, both Sutton and Boveri had realised that the behaviour of chromosomes in meiosis precisely parallels the behaviour of Mendel's genetic particles described some 35 years earlier. In many ways we have witnessed during the past 50 years, and particularly in the last quarter century, a series of exciting breakthroughs in establishing an understanding of genetic function and continuity that are comparable to those of the previous century in demonstrating cellular function and continuity. The determination of the structure of DNA in 1953 and the elucidation of the genetic code throughout the 1960s led to the rapid realisation of the code's universality. The parallel development of sophisticated techniques for studying the genetics of the model bacterium Escherichia coli and its plasmids and viruses paved the way for a new era in biology. We were soon to construct recombinant DNA molecules in vitro, propagate them and eventually express them in E. coli, taking full advantage of the universality of the code. The principles of cloning DNA molecules had been clearly enunciated by Berg and Hogness in the early 1970s, and I myself had the great fortune as a young post-doc to share in this excitement and participate in putting some of these principles into their early practice. By the end of that decade, genes had been cloned from a multitude of eukaryotes and, moreover, technologies had been developed by Maxam and Gilbert and by Sanger that enabled these cloned genes to be sequenced. The accelerating accumulation of knowledge enabled by these simple technical breakthroughs has been astounding, leading to the

determination of the complete genome sequences of budding yeast, the nematode Caenorhabditis elegans and the fruit fly, Drosophila melanogaster, and the prospect of the complete human sequence within a few years. To date we have managed this accumulating wealth reasonably well. Cloned genes have allowed cell biologists access to the encoded proteins, and as a consequence we have a working knowledge of many cellular processes. The sub-cellular meanderings of molecules have been charted with increasing accuracy, and gene products have been positioned in regulatory pathways. The concerted application of genetic and molecular approaches has given new insights into cell biology. This is particularly evident from work on the yeasts, which have come into their own as model systems with our realisation of the extent to which cell biological processes have been conserved. Nevertheless, the resulting regulatory pathways that emerge from our current ways of looking at the cell are rather unidimensional, gene products being placed into linear pathways as a result of either molecular or genetic analyses. Our current views are often blind to the fact that the cell is a multidimensional structure whose components are arranged in space, have multiple contacts that change with time and can respond simultaneously to a multitude of signals. Glimpses of such complexity are emerging from studies in which microarrays of all the identified open reading frames (ORFs) from the complete budding yeast genome have been screened for changes in patterns of gene expression throughout the cell cycle or upon sporulation. Cell-cycle-dependent periodicity was found for 416 of the 6220 monitored ORFs, and over 25% of these genes were found to be clustered at particular chromosomal sites, which suggesting there are global chromosomal responses in transcriptional control (Cho et al., 1998). The study of sporulation is perhaps the first example of the application of this type of technology to a developmental process. It revealed that, of the 6220 genes, about 500 undergo repression and 500 induction in seven temporally distinct patterns during the sporulation process, identifying potential functions

> “Most of the scientists I know are frogs, by which I mean, they will happily lend a hand to their colleagues if their expertise would be helpful in solving an interesting problem.”

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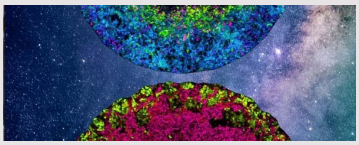

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First person interview - Eryn Dixon

Eryn Dixon is first author of a new Tools & Resources paper that presents a new model system that generates kidney tubule-like structures in a dish. Find out more

for many previously uncharacterised genes (Chu et al., 1998). These studies already reveal layers of complexity in the regulation of the levels of transcripts as cells prepare for and pass through the different stages of meiosis. How much more complex are these patterns likely to be when viewed in terms of proteins, and their interactions, locations and functions within the cell? It seems clear, however, that a wonderful molecular description of the events of meiosis that can match the cytological understanding revealed by the work of Van Beneden and Boveri one hundred years ago is within our grasp. The cataloguing of all cellular proteins is now feasible through a combination of 2D-gel analysis and mass spectrometry, from which molecular mass data can be correlated with the fragment sizes of peptides predicted from whole genome sequence data (the emerging field of proteomics). It is not an easy task, but it seems just a matter of time before we have all this information at our fingertips. Yet how can we know the functions of all these proteins and have a full 3D picture of how they interact within a cell and the dynamics with which they do so? Yeast may be the first eukaryote for which some of these problems can be approached. Its genome is six-times smaller than that of C. elegans and 200 times smaller than the human genome, and has the further advantage that the genes can be easily disrupted through homologous recombination. Thus the prospect of systematic gene deletion to study the function of the 3700 novel ORFs identified in the whole genome sequence is feasible for this organism (Winzeler et al., 1999). One group in particular has devised a multifaceted approach for doing this: the affected gene is simultaneously tagged with an in-frame transcriptional reporter and further modified to epitope tag the affected protein, which thus allows the latter to be immunolocalised within cells (Ross-MacDonald et al., 1999). We can thus see the glimmerings of a holistic, genome-wide, cell-wide unravelling of cellular physiology. Some of these approaches will be easily adaptable to higher organisms. We will soon have read-outs of RNA expression patterns in cells undergoing a

about Eryn and her research in an interview.

variety of developmental and physiological programmes in normal and diseased states. The analysis of function and the identification of ORFs in higher eukaryotes are likely to be more problematic. However, solutions for the rapid assessment of the functions of novel genes are already emerging. New insights are coming from labs using double-stranded RNA to interfere with cellular processes in C. elegans. It was originally found in this organism that the injection of double-stranded RNA corresponding to part of the mRNA of a gene prevents the expression of that gene through a mechanism that currently remains mysterious (Fire, 1999). The technique works extremely well in the nematode and even in the fruit fly, but doubts had been cast as to whether it would ever be valuable in mammals. The recent finding that the technique does indeed work in the mouse may well accelerate programmes to identify gene function by circumventing the particularly lengthy procedures for disruption of mouse genes (Wianny and Zernicka-Goetz, 2000). The multiple layers of complexity revealed by these emerging studies give some indication of the computational power that will be needed to model the cell. Is it now time for a new breed of mathematical biologists to emerge? Our present generation of cellular and molecular biologists have lost sight of some of the basic principles of physical chemistry, and quantitative analyses are done poorly if at all. Should the quantification of reaction kinetics now come out of the traditional domain of enzymology and be applied to multiple cellular processes - if we are truly to understand the dynamics of the living cell? If the yeast cell is complex, then how much greater complexity will we find in multicellular eukaryotes, given all the potential for cell-cell interactions? These problems are perhaps most alluring in the field of development, in which many phenomena are now demanding attention at the cellular level. In recent decades we have seen classical embryological approaches supplemented by genetic analyses to define the components of many developmental signalling pathways. This has demonstrated the existence of a conserved collection of molecular

switches that can be used in a variety of different developmental circumstances. We are perhaps reaching the limits at which conventional genetic analyses can interpret these processes: often the precise relationships between components of regulatory pathways is not clear. We require a better grasp of how the molecules within the pathways interact, which will require the concerted application of sub-cellular fractionation, to identify molecular complexes, and proteomics. This has to be achieved in a way that allows us to interpret the consequences of multiple signalling events between different cell types. In the introduction to his famous text The Cell in Development and Inheritance, E. B. Wilson wrote almost a century ago: 'It has only recently become possible adequately to formulate the great problems of development and heredity in terms of cellular biology - indeed we can as yet do little more than so formulate them.' Has our perspective changed during the past one hundred years? Are not these the same challenges that lie ahead for the twenty-first century? It is now rather like being Alice in Wonderland in a room with many doors, each of which marks the onset of a new journey. Undoubtedly, any of the doors will lead to remarkable opportunities, but to what extent can we, as Alice, rely upon drinking from the bottle, or eating the biscuit, that happens to be at hand? We will have to use the existing resources, but it will be fascinating to see what new ingenuities we can bring to bear to help us on our journey through Wonderland. I have the feeling that we are to witness conceptual challenges to the way we think about cell biology that we cannot yet begin to appreciate…but what I would give to be around in one hundred years time to witness the progress we have made on our journeys!

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